Diels-Alder Reaction of 2-Isopropyl-1, 3-butadiene with 4-Benzyloxy-2-butyn-1-al and Crotonaldehyde[1]

By Atsuaki ARAI and Iwao ICHIKIZAKI

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The formation of two isomeric Diels-Alder adducts may be expected when an asymmetric diene and an asymmetric dienophile interact; however, in most cases the isolation of only one isomer has been reported. Moreover, about certain asymmetric addends of the reaction it has been stated[2] that the substituents in the diene generally produce a high degree of specificity in the direction of addition.

In a research program in this laboratory on the Diels-Alder reactions between asymmetric dienes and asymmetric dienophiles, the direction of the addition of 2-isopropyl-1, 3-butadiene (I) to 4-benzyloxy-2-butyn-1-al (II) as well as to crotonaldehyde (X) has been investigated.

A Diels-Alder reaction carried out by heating I and II at 145~150°C in benzene gave an oily product formulated as $C_{18}H_{22}O_2$, b. p. 132~134°C/3×10^{-3}mmHg, $\lambda_{\max}^{\mathrm{EtOH}}$ 236 mμ, ε, 6800, in a 79% yield. This product afforded two red 2, 4-dinitrophenylhydrazones, III′ (m. p. 197~198°C) and IV′ (m. p. 160~161°C), in a ratio of approximately 2 : 3 and proved also to consist of two isomeric adducts. Similarly, it gave, in nearly a quantitative yield, heterogeneous phenylsemicarbazone, recrystallization of which afforded pure fine needles (IV″) with an m. p. of 183~183.5°C and two low-melting fractions, both of which were apparently heterogeneous yet. On treatment with the Brady reagent followed by fractional crystallization, phenylsemicarbazone IV″ gave homogeneous 2, 4-dinitrophenylhydrazone IV′, and one melted at 156.5~158°C of the heterogeneous phenylsemicarbazones gave the 2,4-dinitrophenylhydrazones, III′ and IV′, in a ratio of approximately 2.5 : 1.

When subjected to a superheated steam distillation over phthalic and sulfuric acids[3,4], the phenylsemicarbazone IV″ was converted into 4-isopropyl-2-methylbenzaldehyde (VI) in a 51% yield, accompanied by the removal of the benzyl alcohol. On similar treatment, the heterogeneous phenylsemicarbazone described above afforded a yellow oily product consisting of 5-isopropyl-2-methylbenzaldehyde (V) and

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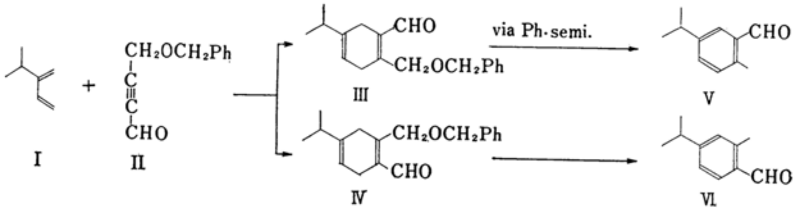
[1] Presented in part at the 13th Annual Meeting of the Cheimcal Society of Japan, Tokyo, April 1960.

[2] A. J. Birch, *Ann. Reports on Prog. Chem.*, 47, 177 (1950).

[3] A. Arai and I. Ichikizaki, This Bulletin, 34, 1571 (1961).

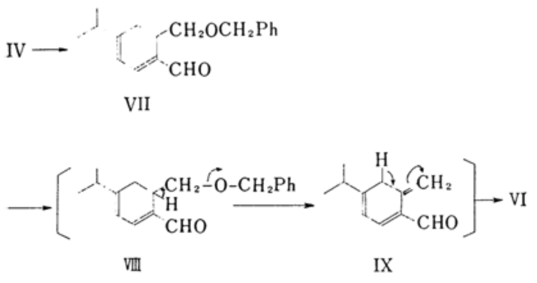
[4] A. Arai and I. Ichikizaki, ibid., 35, 45 (1962).



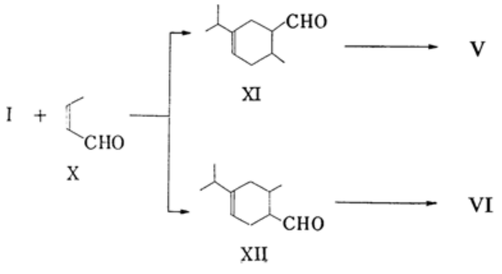
an appreciable amount of VI, both of which were characterized as solid derivatives.

This experimental evidence thus far obtained has made it possible to conclude that the Diels-Alder adduct of I with II consists of 2-benzyloxymethyl-5-isopropylcyclohexa-1, 4-dienylmethanal (III) and 2-benzyloxymethyl-4-isopropylcyclohexa-1, 4-dienylmethanal (IV) in a ratio of approximately 2 : 3.

The original heterogeneous adduct, after being treated with a diluted methanolic sulfuric acid solution at 60°C for 10 min., showed a decrease in the $\varepsilon_{\max}$ to about 74% of the original value of the light-absorption maximum at 236 mμ; it simultaneously indicated the appearance of a maximum at 308 mμ characteristic of an α, β-γ, δ-unsaturated aldehyde system⁵⁾. On prolonged treatment with acid, the isomerized aldehydes, e. g., VII, were finally aromaticized to the corresponding benzaldehydes, e. g., VI, which were indicated by a new maximum shown at 256 mμ. Such acid-catalyzed aromaticization, remarkable for the 2-benzyloxymethylcyclohexa-1, 4-dienealdehyde series⁶⁾, is presumably accelerated by the initial isomerization to the α, β-γ, δ-unsaturated aldehydes, as represented by VII, which readily lose their benzyl alcohol and convert, via labile intermediates, e. g., IX, into the corresponding benzaldehydes.



According to Nazarov and Mavrov⁷⁾, the condensation of I with X carried out at 200°C produces a heterogeneous adduct which is concluded to consist of 3-isopropyl-6-methyl-3-cyclohexenylmethanal (XI) and 4-isopropyl-6-methyl-3-cyclohexenylmethanal (XII) from the fact that terephthalic acid and isophthalic acid can be derived therefrom in a ratio of approximately 1 : 3 by successive oxidative treatments. Some modified methods for the identification and determination of the product in the same Diels-Alder reaction were employed by the present authors. The inseparable reaction product obtained under conditions similar to those cited above was treated with sulfur to give the dehydrogenation product which was determined, by being characterized as the 2, 4-dinitrophenylhydrazones, to consist of 3-isopropyl-6-methylbenzaldehyde (V) and 4-isopropyl-6-methylbenzaldehyde (VI), which apparently came from XI and XII respectively. The proportion of XI to XII could be decided directly by gas-liquid chromatography using a Carbowax-4000 on Celite DM-13A as the column packing material; the value of 1/2.5 was thereby obtained. In connection with the direction of the addition of the diene to the dienophile, it should be noted that the proportion of XII to XI markedly increases, as shown in Tables I and II cited in the experimental section, when the condensation was carried out at a lower temperature.



As described above, the Diels-Alder reaction of I with II as well as with X gave both of the two possible adducts in extremely near proportions, although the predominant direction of the addition conforms to the common rule²⁾. In the condensation with unsymmetrical addends, it has been generally reported that a β-substituted diene, $CH_2=C(X)-CH=CH_2$, reacts with such a dienophile, $R-CH=CH-Y$, containing only a negative group Y as crotonaldehyde to give an adduct with X para to Y. As far as we know, such Diels-Alder dienes as

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5) J. C. Lunt and F. Sondheimer, *J. Chem. Soc.*, **1950**, 3361.

6) Similar aromaticization in this series was also encountered in the cases of acid-catalyzed acetal formation of 2-benzyloxymethyl-4, 5-dimethylcyclohexa-1, 4-dienylmethanal³⁾ and 2-benzyloxymethyl-4, 5, 6-trimethylcyclohexa-1, 4-dienylmethanal⁴⁾.

7) I. N. Nazarov and M. V. Mavrov, *Zhur. Obshchei Khim.*, **29**, 1158 (1959).

2-isopropyl-1, 3-butadiene (I), effecting a remarkable decrease in specificity[8] in the direction of addition, have rarely been found in the literature.

Experimental[11]

2-Isopropyl-1, 3-butadiene (I).—2-Isopropyl-1, 3-butadiene (I) was obtained by repeated fractionation with a 100 cm. modified Todd fractionating column of the dehydration product of 3, 4-dimethyl-1-penten-3-ol[4] and had b. p. 85.5~86.5°C/760 mmHg and n_{D}^{20} 1.4312 (lit. b. p. 85~85.5°C, n_{D}^{20} 1.4316[12]; b. p. 86~87°C, n_{D}^{20} 1.4324[7]).

4-Benzyloxy-2-butyn-1-al (II). — 4-Benzyloxy-2-butyn-1-al (II) was prepared by the method described in a previous paper[3,4] and had b. p. 115~118°C/2 mmHg and n_{D}^{20} 1.5408.

Condensation of I with II.—A mixture of I (13.5 g.), II (22.0 g.) and benzene (4 ml.) was heated with a small amount of hydroquinone for 13 hr. at 145~150°C in a 100 ml. sealed glass tube. Distillation of the reaction product gave an oil (29.0 g.) having b. p. 120~138°C/3×10^{-3} mmHg and n_{D}^{21} 1.5438~1.5454 ; on redistillation this oil afforded an inseparable mixture of the adducts III and IV as a pale yellow oil, b. p. 132~134°C/3×10^{-3} mmHg, n_{D}^{20} 1.5450. $\lambda_{\max}^{\mathrm{EtOH}}$ 236 mμ (ε, 6800).

Found : C, 79.96 ; H, 8.30. Calcd. for $C_{18}H_{22}O_2$: C, 79.96 ; H, 8.20%.

In order to determine the proportion of III to IV in the original adduct, the aldehyde (0.55 g.) was converted on treatment with the Brady reagent into 2, 4-dinitrophenylhydrazone, which was fractionally crystallized from methanol to give red-orange needles, m. p. 197~198°C (III′) (0.27 g.) and red needles, m. p. 160~161°C (IV′) (0.44 g.).

Found : III′: N, 12.36. IV′: N, 12.42. Calcd. for $C_{24}H_{26}O_5N_4$: N, 12.44%.

The aldehyde (20.0 g.) in ethanol (40 ml.) was treated with phenylsemicarbazide (11.0 g.) in the usual manner to afford crude phenylsemicarbazone (28.8 g., 96.6%), which on fractional crystallization from methanol gave colorless fine needles, m. p. 183~183.5°C (IV″) (8.2 g., 28.4% based on the crude crystalline solid), $\lambda_{\max}^{\mathrm{EtOH}}$ 235 mμ (ε, 17200), 284 (34200), and two low-melting fractions which melted at 163~169°C (3.8 g., 13.2%) and 156.5~158°C (15 g., 52.0%), $\lambda_{\max}^{\mathrm{EtOH}}$ 235 mμ (ε, 11600), 284 (22900), both of which were apparently heterogeneous.

Found : IV″ : N, 10.62. The last fraction : N, 10.48. Calcd. for $C_{25}H_{29}O_2N_3$: N, 10.41%.

On treatment with the Brady reagent, the phenylsemicarbazone IV″ gave the homogeneous 2, 4-dinitrophenylhydrazone IV′ in an excellent yield, and the heterogeneous one which melted at 156.5~158°C (2.2 g.), afforded the 2, 4-dinitrophenylhydrazones III′ (1.5 g.) and IV′ (0.6 g.).

Treatment of the Original Adduct Obtained Above with Methanolic Sulfuric Acid.—The original adduct (2.0 g.), dissolved in 70% aqueous methanol (13.5 ml.) containing concentrated sulfuric acid (1.4 g.), was warmed for 10 min. at 60°C. To the resultant solution a saturated methanolic solution of potassium acetate was added drop by drop while the mixture was being cooled, until the precipitation of potassium sulfate was complete. The cooled reaction mixture was then filtered, and the filtrate was extracted with benzene. Distillation of the dried benzene solution gave a pale yellow oil (1.15 g.), b. p. 145~146°C/1.5×10^{-2} mmHg, n_{D}^{28} 1.5481, $\lambda_{\max}^{\mathrm{EtOH}}$ 236 mμ (ε, 5000), 308 (1100).

Found : C, 79.24 ; H, 8.20. Calcd. for $C_{18}H_{22}O_2$: C, 79.96 ; H, 8.20%.

The oil obtained above (1.0 g.) was again treated with a solution of concentrated sulfuric acid (1.0 g.) in 80% aqueous methanol (7 ml.) for 1 hr. at 60°C and successively for 24 hr. at room temperature. The reaction mixture was neutralized with aqueous potassium carbonate, organic material was taken up in ether and the ether layer was washed with water. After removal of the solvent from the dried solution, the residue was distilled to afford a yellow oil (0.6 g.), b. p. 105~135°C/2 $\times10^{-2}$ mmHg, which showed light-absorption maxima at 236, 256 and 308 mμ in ethanol.

Condensation of I with Crotonaldehyde (X).—A mixture of I (2.5 g.), X (1.09 g.) and an appropriate solvent (10 ml.) was heated with a small amount of hydroquinone under the conditions listed in Table I in a 50 ml. glass bomb tube. Removal of the solvent, followed by distillation of the residue through a 7 cm. Vigreux column under nitrogen, afforded an inseparable mixture of the expected adducts, 3-isopropyl-6-methyl-3-cyclohexenylmethanal (XI) and 4-isopropyl-6-methyl-3-cyclohexenylmethanal (XII); the properties of these adducts, their elemental analyses and their proportions, determined by gas-liquid chromatography using a 0.6×200 cm., 30% Carbowax-4000 on Celite DM-13A as the column-packing material, are summarized in Table II.

4-Isopropyl-2-methylbenzaldehyde (VI).—*a) Steam Distillation of the Phenylsemicarbazone IV″ with Acid.*—A mixture of IV″ (4.4 g.), propylene glycol (60 g.), *o*-phthalic acid (4.4 g.), concentrated sulfuric acid (22.0 g.) and water (80 ml.) was distilled under superheated steam until no more organic material passed over. The distillate (1400 ml.) was then extracted with ether, and the ether extract was washed with 10% aqueous sodium carbonate and with water and dried over sodium sulfate. Removal of the solvent, followed by fractionation of the residue, gave a fore-run consisting mainly of benzyl alcohol and 4-isopropyl-2-methylbenzaldeheyde (VI) (0.9 g., 51%) in the form of a pale yellow oil. A redistilled sample had b. p. 123~124°C/17 mmHg and n_{D}^{21} 1.5275. $\lambda_{\max}^{\mathrm{EtOH}}$ 259 mμ.

The semicarbazone crystallized from methanol in

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[8] An asymmetric dienophile, such as β-acetyl acrylic acid[9] and 4-methoxy-β-nitrostyrene[10], possessing two negative groups adjacent to the carbon-carbon double bond will, of course, have the same effect on the direction of the addition of a certain asymmetric diene.

[9] E. Buchta and G. Satzinger, *Chem. Ber.*, **92**, 449 (1959).

[10] W. C. Wildman, R. B. Wildman, W. T. Norton and J. B. Fine, *J. Am. Chem. Soc.*, **75**, 1913 (1953).

[11] All melting points were taken on a Kofler hot-stage microscope and are uncorrected. Ultraviolet spectra were measured on a Hitachi model EPU-2A spectrophotometer.

[12] C. G. Overberger, A. Fischman, C. W. Roberts, L. A. Arond and J. Lal, *J. Am. Chem. Soc.*, **73**, 2540 (1951).

TABLE I. DIELS-ALDER REACTION BETWEEN 2-ISOPROPYL-1,3-BUTADIENE AND CROTONALDEHYDE

Exp. no.	Reaction conditions Temp. °C	Time hr.	Solvent	Total yield of the adduct g.	%
1	125	12	Benzene	1.21	28.0
2	120~125	30	*n*-Hexane	1.20	27.8
3	200	6	Benzene	2.60	60.0
4	200	12	Benzene	2.76	64.0

TABLE II. PROPERTIES AND COMPOSITIONS OF THE ADDUCTS LISTED IN TABLE I

Exp. no.	B. p. °C/mmHg	n_D^T	Found Calcd. for $C_{11}H_{18}O$ C	H	Composition of the adduct* XI	XII
1	73~74/4	1.4710^{20}	79.65 79.46	10.99 10.92	1	8.0
2	70~72/3.5	1.4709^{20}			1	8.5
3	75/4	1.4711^{19}	79.71 79.46	11.00 10.92	1	2.5
4	74~75/4	1.4710^{20}			1	2.6

* The gas-liquid chromatogram of the adduct indicated two peaks, at a retention time of 9.7 and 10.3 min., attributable to the compounds XII and XI respectively and the proportion of XII to XI was calculated from their peak areas column temperature, 200°C; the carrier gas, hydrogen, had a flow rate of 30 ml./min.

needles, m. p. 199~200°C, which yellow rapidly on exposure to the light (lit.[13] m. p. 198~199°C).

Found: N, 19.39. Calcd. for $C_{12}H_{17}ON_3$: N, 19.16%.

The 2,4-dinitrophenylhydrazone crystallized from ethanol-ethyl acetate as red-orange needles, m. p. 184~185°C.

Found: N, 16.42. Calcd. for $C_{17}H_{18}O_4N_4$: N, 16.37%.

b) Sulfur Dehydrogenation of the Adduct Obtained in Exp. 1 Listed in Table I.—The adduct (0.9 g.) was heated under reflux with sulfur (1.3 g.) under a nitrogen atmosphere at 230°C for 45 min. at which time the evolution of hydrogen sulfide ceased. The black reaction mixture was distilled under nitrogen and chromatographed on alumina to give a yellow oil (0.4 g.), which provided only the 2,4-dinitrophenylhydrazone of VI, m. p. 184°C, after two recrystallizations from ethanol-ethyl acetate. No depression was observed in melting point on admixture with the 2,4-dinitrophenylhydrazone prepared in a).

5-Isopropyl-2-methylbenzaldehyde (V).—*a) Steam Distillation of the Heterogeneous Phenylsemicarbazone Melted at 156.5~158°C with Acid.*—A mixture of the phenylsemicarbazone (7.0 g.), propylene glycol (70 ml.), *o*-phthalic acid (7.0 g.), concentrated sulfuric acid (30.0 g.) and water (80 ml.) was distilled in the manner described above. Concentration of the dried ether extract, followed by distillation of the residue under nitrogen, gave a small fore-run, b. p. 90~99°C/16 mmHg, consisting largely of benzyl alcohol and a pale yellow oil (1.8 g.), b. p. 115~118°C/16 mmHg, n_D^{21} 1.5288, which on redistillation through a 10 cm. Vigreux column afforded an oil with b. p. 117~118°C/16 mmHg and n_D^{20} 1.5294.

Found: C, 81.32; H, 8.69. Calcd. for $C_{11}H_{14}O$: C, 81.44; H, 8.70%.

The oil obtained above was treated with semicarbazide acetate in methanol to give, after being crystallized from ethanol, the semicarbazone of V, m. p. 169~170°C (lit.[14] m. p. 170~171°C), and an appreciable amount of that of VI, m.p. 198~199°C; the latter exhibited no melting point depression on admixture with that of authentic VI.

Found (for semicarbazone of V): N, 19.29. Calcd. for $C_{12}H_{17}ON_3$: N, 19.16%.

Treatment of this oil with the Brady reagent afforded, after fractional crystallization from ethanol-ethyl acetate, the 2,4-dinitrophenylhydrazone of V, m. p. 193~194°C (lit.[14] m. p. 190~191°C) as brightly red plates.

Found: N, 16.64. Calcd. for $C_{17}H_{18}O_4N_4$: N, 16.37%.

From the soluble fraction, a small amount of the 2,4-dinitrophenylhydrazone of VI, m. p. 183~184°C, was obtained. It exhibited no melting point depression on admixture with the 2,4-dinitrophenylhydrazone prepared from authentic VI.

b) Sulfur Dehydrogenation of the Adduct Obtained in Exp. 3 Listed in Table I.—The adduct (2.0 g.) was heated under reflux with sulfur (1.5 g.) under the same conditions as have been described for the preparation of 4-isopropyl-2-methylbenzaldehyde (VI). The distillate obtained by simple distillation of the reaction mixture was converted into the crude 2,4-dinitrophenylhydrazone (1.32 g.); this, on fractional crystallization from ethanol-ethyl acetate, afforded the 2,4-dinitrophenylhydrazone of VI (0.45 g.), m. p. 184~185°C, and of V (0.35 g.), m. p. 192~193°C, both of which exhibited no melting point depression on admixture with those prepared from authentic VI and V respectively.

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[13] P. Chuit and J. Bolle, *Bull. soc. chim.*, **35**, 200 (1924).

[14] C. T. Lester, R. E. Donaldson and J. C. Oswald, *J. Am. Chem. Soc.*, **71**, 1502 (1949).

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Laboratory of Organic Chemistry
Kobayasi Institute of Physical Research
Kokubunji, Tokyo